III. AMENDMENTS TO CLAIMS

Please amend, as set forth below, claims 5, 13, 14, 29, 34, 39, 40, 41 52, 56, 61 and 65. Please cancel claim 64 without prejudice.

IN THE CLAIMS:

1. *(Previously Presented)* A method for screening an individual for primary colorectal cancer, the method comprising:

a) determining a total concentration of TIMP-1 in a plasma sample of said individual;

b) constructing a percentile plot of total plasma TIMP-1 concentrations obtained from a non-colorectal cancer population;

c) constructing a ROC (receiver operating characteristics) curve based on total plasma TIMP-1 concentrations determined in a non-colorectal cancer population and on total plasma TIMP-1 concentrations determined in a primary colorectal cancer population;

d) selecting a desired sensitivity;

e) determining from the ROC curve the specificity corresponding to the desired sensitivity;

f) determining from the percentile plot the total plasma TIMP-1 concentration value corresponding to the determined specificity; and

g) indicating the individual as likely to have primary colorectal cancer if the total concentration of TIMP-1 in the plasma sample of the individual is equal to or higher than said total plasma TIMP-1 concentration value corresponding to the determined specificity and indicating the individual as unlikely to have primary colorectal cancer if the total concentration of TIMP-1 in the plasma sample of the individual is lower than

said total plasma TIMP-1 concentration value corresponding to the determined specificity.

Claims 2-4 (Cancelled)

5. *(Currently Amended)* A method according to claim 41, 56 or 61, wherein the combining the total concentration of TIMP-1 in the plasma sample of the individual with the concentration of free TIMP-1 in the plasma sample of the individual to result in the combined parameter of the individual and the combining the total plasma TIMP-1 concentration of the non-colorectal cancer population with the free plasma TIMP-1 concentration of the non-colorectal cancer population to result in the benchmark combined parameter are performed by logistic regression analysis.

6. *(Withdrawn)* A method according to claims 1 or 5, which comprises additionally determining at least one second parameter, the second parameter representing the concentration of an additional tumour marker different from any form of TIMP-1, in a body fluid sample from the individual.

Claim 7 (Cancelled).

8. *(Withdrawn)* A method according to claim 6, wherein the combining is performed by logistic regression analysis.

Claim 9 (Cancelled)

Claim 10 (Cancelled)

11. *(Withdrawn)* A method according to claim 9, wherein the tumour marker is selected from the group consisting of CEA, soluble U-PAR, cathepsin B, HER2-neu, CA15-3 and YKL-40.

12. *(Withdrawn)* A method according to claim 11, wherein the at least one second parameter determined is the concentration of CEA.

13. *(Currently Amended)* A method according to claims 1, 41, 55, 56, 60 or 61 ~~or 5~~, wherein the individual is a member of a population not already identified as having an increased risk of developing primary colorectal cancer.

14. *(Currently Amended)* A method according to claims 1, 41, 55, 56, 60 or 61 ~~or 5~~,wherein the individual is a member of a population already identified as having an increased risk of developing primary colorectal cancer.

Claims 15-19 (Cancelled).

20. *(Withdrawn)* A method according to claims 15 or 19, which comprises additionally determining at least one second parameter, the second parameter representing the concentration of an additional tumour marker different from any form of TIMP-1, in a body fluid sample from the individual.

Claim 21 (Cancelled).

22. *(Withdrawn)* A method according to claim 21, wherein the combining is performed by logistic regression analysis.

23. *(Withdrawn)* A method according to claim 21, wherein the discriminating value of the combined parameter is a value which has been determined by determining said combined parameter in both a healthy control population and a population with known metastatic cancer, thereby determining the discriminating value which identifies the metastatic cancer population with a predetermined specificity or a predetermined sensitivity.

Claim 24 (Cancelled).

25. *(Withdrawn)* A method according to claim 20, wherein the tumour marker is selected from the group consisting of CEA, soluble u-PAR, cathepsin B, HER2-neu, CA15-3 and YKL-40.

26. *(Withdrawn)* A method according to claim 25, wherein the at least one second parameter determined is the concentration of CEA.

Claims 27-28 (Cancelled)

29. *(Currently Amended)* A method according to claim 1, 41, 55, 56, 60 or 61 ~~or 5~~, wherein the primary colorectal cancer is selected from the group consisting of colon cancer Dukes' stage A, colon cancer Dukes' stage B, colon cancer Dukes' stage C, rectal cancer Dukes' stage A, rectal cancer Dukes' stage B and rectal cancer Dukes' stage C.

Claims 30-33 (Cancelled).

34. *(Currently Amended)* A method according to claim 1, 41, 55, 56, 60 or 61, wherein the determination of the total concentration of TIMP-1 in a plasma sample of the individual is performed by means of an immuno assay or an activity assay.

35. *(Original)* A method according to claim 34, wherein the immuno assay is an ELISA.

36. *(Original)* A method according to claim 34, wherein the activity assay is zymography.

Claim 37-38 (Cancelled).

39. *(Currently Amended)* A method according to claim 1, 41, 55, 56, 60 or 61, wherein the colorectal cancer is colon cancer.

40. *(Currently Amended)* A method according to claim 1, 41, 55, 56, 60 or 61, wherein the colorectal cancer is rectal cancer.

41. (*Currently Amended)* A method for screening an individual for primary colorectal cancer, the method comprising:

a) determining a total concentration of TIMP-1 in a plasma sample of said individual, and a concentration of free TIMP-1 in a plasma sample of said individual;

b) combining the total concentration of TIMP-1 in the plasma sample of the individual with the concentration of free TIMP-1 in the plasma sample of the individual to result in a combined parameter of the individual;

c) combining a total plasma TIMP-1 concentration of a non-colorectal cancer population with a free plasma TIMP-1 concentration of the non-colorectal cancer population , the resulting combination being referred to herein as ~~to result in~~ a non-colorectal cancer benchmark combined parameter;

d) combining a total plasma TIMP-1 concentration of a primary colorectal cancer population with a free plasma TIMP-1 concentration of the primary colorectal cancer population, the resulting combination being referred to herein as ~~to result in~~ a primary colorectal cancer benchmark combined parameter;

e) constructing a percentile plot of the non-colorectal cancer benchmark combined parameter;

f) constructing a ROC (receiver operating characteristics) curve based on the non-colorectal cancer benchmark combined parameter and the primary colorectal cancer benchmark combined parameter;

g) selecting a desired sensitivity;

h) determining from the ROC curve the specificity corresponding to the desired sensitivity;

i) determining from the percentile plot the non-colorectal cancer benchmark combined parameter value corresponding to the determined specificity; and

j) indicating the individual as likely to have primary colorectal cancer if the combined parameter of the individual is equal to or higher than said non-colorectal

cancer benchmark combined parameter value corresponding to the determined specificity and indicating the individual as unlikely to have primary colorectal cancer if the combined parameter of the individual is lower than said non-colorectal cancer benchmark combined parameter value corresponding to the determined specificity.

Claim 42 (Cancelled).

43. *(Withdrawn)* A method according to claim 6, wherein the additional tumour marker is a colorectal tumour marker.

Claim 44 (Cancelled).

45. *(Withdrawn)* A method according to claim 44, wherein the combining is performed by logistic regression analysis.

Claim 46 (Cancelled).

47. *(Withdrawn)* A method according to claim 46, wherein the tumour marker is selected from the group consisting of CEA, soluble U-PAR, cathepsin B, HER2-neu, CA15-3 and YKL-40.

48. *(Withdrawn)* A method according to claim 47, wherein the at least one second parameter determined is the concentration of CEA.

49. *(Withdrawn)* A method according to claim 43, wherein the individual is a member of an unselected population.

50. *(Withdrawn)* A method according to claim 43, wherein the individual is a member of a population already identified as having an increased risk of developing cancer.

51. (*Previously Presented*) A method according to claim 14, wherein the individual has a genetic disposition for primary colorectal cancer, has been exposed to carcinogenic substances or has a primary colorectal cancer-predisposing or non-malignant diseases.

52. *(Currently Amended)* A method according to claim 14, wherein the individual is selected from the group consisting of: an individual who had a ~~prior~~ polyp, an individual with Crohn's disease, an individual with an ulcerative colitis, ~~or~~ and an individual with one or more family members with colorectal cancer.

53. *(Withdrawn)* A method according to claim 50, wherein the individual has a genetic disposition for cancer, has been exposed to carcinogenic substances or has a cancer-predisposing or non-malignant diseases.

54. *(Withdrawn)* A method according to claim 50, wherein the individual is selected from the group consisting of: an individual who had a prior polyp, an individual with Crohn's disease, an individual with an ulcerative colitis, an individual with one or more family members with colorectal cancer, or an individual with a resection of early colorectal cancer.

55. *(Previously Presented)* A method for screening an individual for primary colorectal cancer, the method comprising:

a) determining a total concentration of TIMP-1 in a plasma sample of said individual;

b) constructing a percentile plot of total plasma TIMP-1 concentrations obtained from a non-colorectal cancer population;

c) selecting a desired specificity;

d) determining from the percentile plot the total plasma TIMP-1 concentration value corresponding to the desired specificity; and

e) indicating the individual as likely to have primary colorectal cancer if the total concentration of TIMP-1 in the plasma sample of the individual is equal to or higher than said total plasma TIMP-1 concentration value corresponding to the desired specificity and indicating the individual as unlikely to have primary colorectal cancer if the total

concentration of TIMP-1 in the plasma sample of the individual is lower than said total plasma TIMP-1 concentration value corresponding to the desired specificity.

56. *(Currently Amended)* A method for screening an individual for primary colorectal cancer, the method comprising:

a) determining a total concentration of TIMP-1 in a plasma sample of said individual and a concentration of free TIMP-1 in a plasma sample of said individual;

b) combining the total concentration of TIMP-1 in the plasma sample of said individual with the concentration of free TIMP-1 in the plasma sample of said individual to result in a combined parameter of the individual;

c) combining a total plasma TIMP-1 concentration of a non-colorectal cancer population with a free plasma TIMP-1 concentration of the non-colorectal cancer population, the resulting combination being referred to herein as ~~to result in~~ a non-colorectal cancer benchmark combined parameter;

d) constructing a percentile plot of the non-colorectal cancer benchmark combined parameter;

e) selecting a desired specificity;

f) determining from the percentile plot the non-colorectal cancer benchmark combined parameter value corresponding to the desired specificity; and

g) indicating the individual as likely to have primary colorectal cancer if the combined parameter of the individual is equal to or higher than said non-colorectal cancer benchmark combined parameter value corresponding to the desired specificity and indicating the individual as unlikely to have primary colorectal cancer if the combined parameter of the individual is lower than said non-colorectal cancer benchmark combined parameter value corresponding to the desired specificity.

Claims 57-58 (Cancelled)

59. *(Previously Presented)* A method according to claims 1,41, 55, 56, 60, or 61, wherein the total concentration of TIMP-1 comprises the sum of the TIMP-1 in free form and the TIMP-1 in complex forms.

60. *(Previously Presented)* A method for screening an individual for primary colorectal cancer, the method comprising determining a total concentration of TIMP-1 in a plasma sample of said individual, and indicating the individual as likely to have primary colorectal cancer if the total concentration of TIMP-1 in the plasma sample of the individual is equal to or higher than the total concentration of TIMP-1 measured in plasma in a non-colorectal cancer population, and indicating the individual as unlikely to have primary colorectal cancer if the total concentration of TIMP-1 in the plasma sample of the individual is lower than the total concentration of TIMP-1 measured in plasma in a non-colorectal cancer population.

61. *(Currently Amended)* A method for screening an individual for primary colorectal cancer, the method comprising:

a) determining a total concentration of TIMP-1 in a plasma sample of said individual and a concentration of free TIMP-1 in a plasma sample of said individual;

b) combining the total concentration of TIMP-1 in the plasma sample of the individual with the concentration of free TIMP-1 in the plasma sample of said individual to result in a combined parameter of the individual;

c) combining a total plasma TIMP-1 concentration of a non-colorectal cancer population with a free plasma TIMP-1 concentration of the non-colorectal cancer population, the resulting combination being referred to herein as ~~to result in~~ a non-colorectal cancer benchmark combined parameter;

d) and indicating the individual as likely to have primary colorectal cancer if the combined parameter of the individual is equal to or higher than the non-colorectal cancer benchmark combined parameter, and indicating the individual as unlikely to

have primary colorectal cancer if the combined parameter of the individual is lower than the non-colorectal cancer benchmark combined parameter.

Claims 62-63 (Cancelled)

Claim 64 (Cancelled)

65. (*Currently Amended*) A method according to claim 41,56 or 61 wherein the total plasma TIMP-1 concentration of the non-colorectal cancer population and the free plasma TIMP-1 concentration of the non-colorectal cancer population are determined prior to the sub-section c).